

solved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamically stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions. The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

Example 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

| | Composition I wt % | Composition II wt % |
|--|-----------------------|------------------------|
| Cyclosporin | 0.1 | 0.05 |
| Castor Oil | 1.25 | 1.25 |
| Polysorbate 80 | 1.00 | 1.00 |
| Premulen ® | 0.05 | 0.05 |
| Glycerine | 2.20 | 2.20 |
| Sodium hydroxide | qs | qs |
| Purified Water | qs | qs |
| pH | 7.2-7.6 | 7.2-7.6 |
| Weight Ratio of Cyclosporin A to Castor Oil | 0.08 | 0.04 |

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I.

This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

What is claimed is:

1. A topical ophthalmic emulsion for treating an eye of a human having keratoconjunctivitis sicca, wherein the topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is therapeutically effective in treating keratoconjunctivitis sicca.

2. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion further comprises a tonicity agent or a demulcent component.

3. The topical ophthalmic emulsion of claim 2, wherein the tonicity agent or the demulcent component is glycerine.

4. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion further comprises a buffer.

5. The topical ophthalmic emulsion of claim 4, wherein the buffer is sodium hydroxide.

6. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

7. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

8. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.